

# Durable response of breast cancer leptomeningeal metastasis to capecitabine monotherapy

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We report a durable (12-month) response to capecitabine monotherapy, shown clinically, by MRI, and by cerebrospinal fluid analysis, in a patient with leptomeningeal metastasis from breast cancer. *Neuro-Oncology* 6, 63–64, 2004 (Posted to *Neuro-Oncology* [serial online], Doc. 03-033, October 15, 2003. URL <http://neuro-oncology.mc.duke.edu>; DOI: 10.1215/S1152 8517 03 00033 4)

Leptomeningeal metastasis (LM)<sup>2</sup> develops in up to 5% of patients with breast cancer. It causes neurological disability and death because of damage to the brain, cranial nerves, and spine. Standard therapy for LM consists of radiotherapy to symptomatic sites within the neuraxis and/or intra-cerebrospinal fluid (intra-CSF) chemotherapy. The role of systemic chemotherapy for LM is not well defined. We report a patient with breast cancer and diffuse LM who demonstrated clinical, neuroimaging, and CSF response to capecitabine (Xeloda, Roche Laboratories, Nutley, NJ) monotherapy at 12 months.

## Case Study

A 42-year-old woman with a medical history significant for hypertension and type II diabetes was diagnosed with stage II estrogen-receptor-positive breast cancer 11 years earlier. Treatment at that time included mastectomy,

chemotherapy (cyclophosphamide, doxorubicin, fluorouracil), and tamoxifen. After 6 years she had recurrence in the left supraclavicular lymph nodes. She was treated with Adriamycin (Pharmacia & Upjohn Company, Kalamazoo, MI) and paclitaxel followed by high-dose chemotherapy and autologous bone marrow transplant. Six months after the transplant, a bone scan demonstrated disease progression, and she received sternal radiation and subsequently vinorelbine, gemcitabine, and finally 3-week cycles of capecitabine monotherapy (1000 mg twice daily for 2 weeks followed by 1 week of rest). The patient remained stable for 8 months and tolerated capecitabine well except for dryness of the palms and soles. Capecitabine was then discontinued because of anemia (hemoglobin 7g/dl). She received radiation to the left femur and pelvis. Three months later she noted blurred vision and progressively worsening headaches. She developed low back pain and diffuse bilateral leg pain. Neurologic examination revealed bilateral papilledema and limb areflexia. Enhanced brain MRI showed abnormal enhancement of both optic nerve sheaths and the meninges of the cerebellum, occipital lobes, and right frontal lobe. There was also diffuse skull metastasis. Enhanced spine MRI showed diffuse linear enhancement of the meninges of the cervical and thoracic cord and the lumbar nerve roots and diffuse vertebral metastasis. CSF examination by lumbar puncture showed elevated opening pressure at 44 cm, elevated white blood cell count (29/mm<sup>3</sup>) and protein concentration (85 mg/dl), reduced glucose concentration (33 mg/dl), and malignant cells.

She was restarted on the same 3-week schedule of capecitabine at 1000 mg twice daily. It was well tolerated, and after 2 months the dose was increased to 1500 mg twice daily. Anemia was initially treated with red blood transfusions and erythropoietin injections, which

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<sup>2</sup> Abbreviations used are as follows: CSF, cerebrospinal fluid; LM, leptomeningeal metastasis.

raised the hemoglobin to 9.5 g/dl. Repeat CSF examination 2, 5, and 10 months after re-initiation of capecitabine demonstrated no malignant cells in the CSF and complete normalization of white blood cell count, as well as protein and glucose concentrations. Her neurological symptoms resolved except for blurred vision in the right eye. Neuraxis MRI showed complete disappearance of spinal meningeal enhancement and reduction in the optic nerve and brain enhancement except for the right frontal lobe. She stayed on capecitabine and did not require erythropoietin injections for the last 6 months of therapy. At the last follow-up at 1 year, she is fully active and has no complaints except for reduced right eye vision. An orbital metastasis was then detected on MRI, for which she is receiving radiation.

## Discussion

Optimal therapy for LM of breast cancer is not defined. In a high percentage of patients, LM develops while patients are on systemic treatment, suggesting that the CSF is a sanctuary from systemic chemotherapy (Chamberlain, 1992; Grossman and Krabak, 1999). For this reason, typical treatment is radiotherapy to symptomatic sites and/or intra-CSF chemotherapy administration. However, intra-CSF chemotherapy has only limited success in LM of breast cancer. A recent trial of intrathecal sustained release cytarabine produced a response rate of only 28%, with a median survival of 88 days (Jaeckle et al., 2001). Siegal (1998) advocates the use of systemic chemotherapy to treat LM, but it is not standard therapy. Ours is the first reported case that we are aware of in which capecitabine alone was used to treat LM.

We selected capecitabine for several reasons. Because the patient's neurological symptoms developed shortly after capecitabine was discontinued, we postulated that

the drug may have effectively prevented or treated LM while it was being administered. In addition, because of the risk of myelosuppression from radiation to all sites of leptomeningeal disease, we withheld radiation. We sought treatment other than intra-CSF chemotherapy because of her excellent performance status. The durable clinical, MRI, and CSF response she demonstrates at 12 months is unexpected. Boogerd et al. (1991) developed a prognostic index of survival in breast cancer LM patients, based on clinical factors and irrespective of treatment. According to this index, her predicted survival is less than 3 months.

Capecitabine is an oral prodrug of fluorouracil used in the palliative treatment of metastatic breast cancer that is resistant to taxane and anthracycline chemotherapy. Animal studies demonstrate that capecitabine and its metabolites cross the blood-brain barrier in very limited quantities (McEvoy, 2002). A study in humans using a fluoropyrimidine similar to capecitabine found that fluorouracil concentrations in CSF were only 1% to 3% of plasma concentrations (Heier et al., 1986). We do not know the mechanism by which our patient responded, but a similar rapid and durable response to capecitabine was reported in a patient with refractory brain metastasis from breast cancer (Wang et al., 2001). It is possible that diffuse leptomeningeal metastasis in our patient disrupted the blood-CSF barrier and allowed a higher than normal concentration in the CSF. Capecitabine without concurrent radiotherapy and intraventricular chemotherapy may be effective in treating LM. Clinical studies are needed to assess the role of capecitabine in the treatment of LM.

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